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WO 2003/086470 A3

(54) Title: SMAC-PEPTIDES AS THERAPEUTICS AGAINST CANCER AND AUTOIMMUNE DISEASES

(57) Abstract: The invention is directed to the use of Smac to sensitize different tumors and self-reactive immune cells to various pro-apoptotic stimuli, in that the cells subsequently undergo apoptosis. Therefore, Smac can be used as a compound for the manufacture of a medicament for the treatment of cancer and autoimmune diseases. Sensitization of the cells is achieved either by applying a cell-permeable form of Smac combined with known anticancer agents or by overexpression of the protein. It is an object of the invention to provide a new method in cancer and autoimmune disease therapy by using Smac agonists for apoptosis regulation. Thus, Smac agonists represent novel promising cancer and autoimmune disease therapeutics to potentiate the efficacy of cytotoxic therapies even in resistant tumors and immune cells.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/04039

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C12N15/12	C12N15/62	A61K47/48	C07K5/103	C07K19/00
	C07K14/47	A61K38/17	C07K5/10	A61K41/00	

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 02/16418 A (THOMAS JEFFERSON UNIVERSITY, USA) 28 February 2002 (2002-02-28) examples claims	1-11, 13-36
X	WO 02/16402 A (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM, USA) 28 February 2002 (2002-02-28) examples claims	1-36
X	WO 02/26775 A (TRUSTEES OF PRINCETON UNIVERSITY, USA) 4 April 2002 (2002-04-04) examples claims	1-11, 13-36

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 March 2004

Date of mailing of the international search report

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International Application No  
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Y	WO 00/58488 A (DALBY BRIAN ;INVITROGEN CORP (US); BENNETT ROBERT P (US)) 5 October 2000 (2000-10-05) examples claims -----	1-11, 13-36
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Y	WO 00/29427 A (CYCLACEL LTD ;FISCHER M PETER (GB); ZHELEV NIKOLAI (GB)) 25 May 2000 (2000-05-25) examples claims -----	1-11, 13-36
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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/04039

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>SCHWARZE S ET AL: "In vivo protein transduction: delivery of a biologically active protein into the mouse"  SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US,  vol. 285, no. 5433,  3 September 1999 (1999-09-03), pages 1569-1572, XP002140133  ISSN: 0036-8075  abstract  page 1571</p> <p>-----</p> <p>FISCHER P M ET AL: "STRUCTURE-ACTIVITY RELATIONSHIP OF TRUNCATED AND SUBSTITUTED ANALOGUES OF THE INTRACELLULAR DELIVERY VECTOR PENETRATIN"  JOURNAL OF PEPTIDE RESEARCH, MUNKSGAARD INTERNATIONAL PUBLISHERS, COPENHAGEN, DK,  vol. 55, no. 2, February 2000 (2000-02),  pages 163-172, XP000899124  ISSN: 1397-002X  the whole document</p> <p>-----</p>	1-11, 13-36
X	<p>FULDA SIMONE ET AL: "Release of Smac from mitochondria bypasses the Bcl-2 inhibition in type II cells and sensitizes for death receptor or drug-induced apoptosis."  PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING,  vol. 42, March 2001 (2001-03), page 552,  XP002251122  ISSN: 0197-016X  abstract  &amp; 92nd Annual Meeting of the American Association for Cancer Research; New Orleans, LA, USA; March 24-28, 2001  abstract</p> <p>-----</p>	1-11, 13-36
X	<p>FULDA SIMONE ET AL: "Smac release from mitochondria bypasses the Bcl-2 inhibition and sensitizes tumor cells for death receptor or drug-induced apoptosis."  BLOOD NOVEMBER 16, 2001,  vol. 98, no. 11 Part 1,  16 November 2001 (2001-11-16), pages 572a-573a, XP002251123  ISSN: 0006-4971  abstract  &amp; 43RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF HEMATOLOGY, PART 1,  7 December 2001 (2001-12-07),  ORLANDO, FLORIDA, USA</p> <p>-----</p>	1-11, 13-36
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## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/EP 03/04039

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FULDA SIMONE ET AL: "Smac peptides or Smac gene transfer as a novel strategy to overcome resistance against TRAIL- or drug-induced apoptosis." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 43, March 2002 (2002-03), pages 527-528, XP002251124 ISSN: 0197-016X abstract & 93rd Annual Meeting of the American Association for Cancer Research; San Francisco, California, USA; April 06-10, 2002 abstract	1-11, 13-36
A	JOHNSTONE RICKY W ET AL: "Apoptosis: A link between cancer genetics and chemotherapy." CELL, vol. 108, no. 2, 25 January 2002 (2002-01-25), pages 153-164, XP002251125 ISSN: 0092-8674 figure 2	1-11, 13-36
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Y	US 6 306 613 B1 (BAIRD ANDREW ET AL) 23 October 2001 (2001-10-23) column 63; example 16	1-11, 13-36
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## INTERNATIONAL SEARCH REPORT

International Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 903 408 A (BIOGEN INC) 24 March 1999 (1999-03-24) figures 3,7 -----	1-11, 13-36
Y	WO 94/04686 A (BARSOUM JAMES G ; BIOGEN INC (US); FAWELL STEPHEN E (US); PEPINSKY R B) 3 March 1994 (1994-03-03) examples 2,4,5,7,13,16 claims 3,16,18,21 -----	1-11, 13-36
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X	SRINIVASULA S M ET AL: "A conserved XIAP-interaction motif in caspase-9 and Smac/DIABLO regulates caspase activity and apoptosis" NATURE, vol. 410, 1 March 2001 (2001-03-01), pages 112-116, XP002962286 ISSN: 0028-0836 abstract; figures -----	1-36

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/04039

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>VERHAGEN A M ET AL: "HtrA2 promotes cell death through its serine protease activity and its ability to antagonize inhibitor of apoptosis proteins"          JOURNAL OF BIOLOGICAL CHEMISTRY,          vol. 277, no. 1,          4 January 2002 (2002-01-04), pages          445-454, XP002957689          ISSN: 0021-9258          page 445          figures          page 453, paragraph DISCUSSION – page 454          -----</p>	1-36
Y	<p>HOLCIK M ET AL: "TRANSLATION UPREGULATION OF X-LINKED INHIBITOR OF APOPTOSIS (XIAP) INCREASES RESISTANCE TO RADIATION INDUCED CELL DEATH"          ONCOGENE,          vol. 19, no. 36,          24 August 2000 (2000-08-24), pages          4174-4177, XP008007068          ISSN: 0950-9232          the whole document          -----</p>	1-36
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## INTERNATIONAL SEARCH REPORT

International application No.  
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### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 1-36 in part because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-36 in part

Present claims 1-36 relate to an extremely large number of possible compounds, as well as their use. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only the expression of the Smac protein. For the protein-carrier combination, no actual example is given. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds specifically prepared in the examples.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10 in part, 11 and 13-36

The Smac/carrier entity as claimed, optionally in combination with another cytostatic agent, a medicament for the treatment of cancer containing it, its use in the treatment of autoimmune disease, and the use of an expression plasmid carrying the gene of the Smac protein as claimed for the treatment of cancer

1.1. claims: 1-10 in part, 25

The Smac/carrier entity as claimed, and a medicament for the treatment of cancer containing it.

1.2. claims: 11, 13-24

Use of the Smac/carrier entity as claimed in combination with another anticancer agent, in the treatment of cancer

1.3. claims: 26-28

Use of the Smac/carrier entity as claimed in the treatment of autoimmune diseases

1.4. claims: 29-36

Use of an expression plasmid carrying the gene of the Smac protein as claimed for the treatment of cancer

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2. claims: 1-10 in part, and 12

The Smac/carrier entity as claimed in combination with radiation therapy, for use as pharmaceutical

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/EP 03/04039

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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